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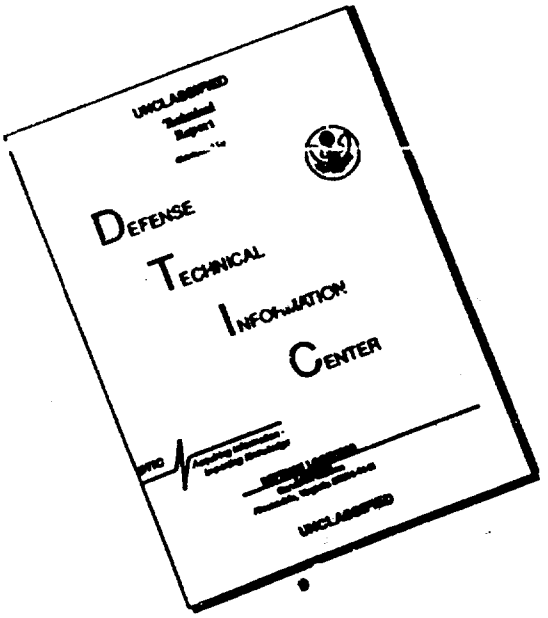

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EVALUATION OF TULAREMIA DUST VACCINE TESTING

- USSR -

[Following is a translation of an article by N. I. Aleksandrov, N. Ye. Gefen, K. G. Capochko, N. S. Garin, G. Ya. Gordon, M. I. Kozhushko, G. P. Korenev, Ye. S. Lazareva, Ye. P. Leykekhman, A. I. Maslov, G. A. Pavlov, N. D. Polivanov, P. S. Romanov, M. G. Rybakov, M. F. Samokhvalov, M. S. Smirnov, M. A. Shtern and V. N. Chepkov in the Russian-language periodical Zhurnal microbiologii, epidemiologii i immunobiologii (Magazine of Microbiology, Epidemiology and Immunobiology), Volume 41, Number 2, Moscow, 1964, pages 38-43.]

In 1958 and 1959, aerosol immunization of small groups of people (156 persons) with tularemia dust vaccine was carried out with favorable results. ~~In 1961 and 1962~~ A study of a method of aerosol immunization with tularemia dust vaccine was conducted with a larger contingent of people.

The aerosol immunization of the people was done in ordinary rooms. Depending on their capacity, from 17 to 297 persons were vaccinated at one time. The duration of each exposure to aerosol immunization was 15 minutes.

Before immunization, a part of the people (468 persons) underwent dispensary examination, including medical inspection, clinical analyses of the blood and urine, X-ray examination of the organs of the chest, as well as an examination with the help of an intracutaneous allergic test with tularin (988 persons) and agglutination reaction (445 persons). The second group of individuals (2,400 persons) did not undergo dispensary examination and the aerosol vaccination was carried out on the basis of information about their health on hand at the medical points. Immediately after immunization, daily medical observation was begun of the state of health of the innoculated persons carried out over a period of 14 days. At the present time all those innoculated have already been under medical control for more than a year.

Besides the physical examination, 463 persons from among those innoculated were put through X-Ray examination at intervals of 1, 3 to 4, 7, 15 and 30 days after aerosol immunization and a clinical analysis of the blood was made on 317 persons in these same periods of time.

The individuals showing post-vaccination reactions were examined according to a special plan which, besides a daily physical examination, provided for measurement of the body temperature every four hours, electrocardiographic and X-ray examination, clinical analysis of the blood, urine and sputum, biochemical studies of the blood (sugar, residual nitrogen, protein fractions and histamine), oxyhemometry and determination of the indices for maximal ventilation of the lungs.

The post-vaccination reactions were classified as weak, moderate and strong according to the degree of manifestation. To weak reactions belonged those cases with a partial loss of the capacity to work and an increase in body temperature to 37.5 degrees; to reactions of moderate strength, the cases with loss of the capacity to work and an increase of body temperature to 38.5 degrees in 24 hours; and to strong reactions the cases with loss of the capacity to work for two or more days, a body temperature higher than 38.5 degrees and a fever lasting more than two days.

In all, 3,385 persons (See Table 1) were innoculated during the period 1957 through 1962 against tularemia by the aerosol method. The immunized contingents differed by a dissimilar initial immunological state. Thus, 933 persons before aerosol immunization had negative sero-allergic reactions for tularemia, positive sero-allergic reactions were found in 42 persons and 2,410 persons were immunized by the aerosol method without preliminary immunological examination.

The frequency and severity of the post-vaccination reactions were in sharp dependence upon the initial immunological background.

It turned out that in individuals having a "clean" background post-vaccination reactions were observed considerably more seldom, were characterized by a much easier course, short duration and were seldom accompanied by a loss in capacity to work. The immunization of individuals with positive sero-allergic reactions was accompanied by much more frequent and strong post-vaccination reactions. However, in spite of the great frequency and manifestation of the post-vaccination reactions, all of the innoculations ended in full recovery in two to four days.

In individuals who were not preliminarily examined, the vaccination caused a relatively low rate of reaction.

Research which was conducted established the dependence of the

reactogenic nature upon the inhaled dose of vaccine. Thus, when immunizing the group with the negative immunological background with optimal doses of 5.5 to 28 million microbes, general reactions were registered by 1.19 per cent of the vaccinated persons at a time when the administration of 130 to 320 million resulted in an increase in the number of general reactions up to 24.2 per cent. Vaccination on a positive sero-allergic background with doses of 1 to 28 million microbes caused the appearance of general reactions in 28.5 per cent of those innoculated. Thereby, in individuals immunized with doses of 1 to 4.6 million microbes, general reactions were observed in 23.2 per cent, and among those innoculated with doses of 5.5 to 28 million microbes in 41.5 per cent.

The effectiveness of aerosol and cutaneous immunization of tularemia vaccine was evaluated according to the agglutination reaction and the intracutaneous allergy test with tularin. Reactions were produced according to the generally accepted methodology in 15 to 20, 30 to 41, 90 to 110, 180 and 360 days after immunization. Only the individuals were examined whose sero-allergic reactions before vaccination had been negative.

The immunological effectiveness of the tularemia vaccine was studied depending on the inhaled dose of the preparation (See Table 2).

As is known, the titers of the agglutinins do not reflect the intensity of the immunity during tularemia; however, they are evidence of the immunological improvements in the organism of the innoculated persons in answer to the administration of the vaccines. Therefore, a comparison of the dynamics for the titers of the agglutinins gives some idea of the effectiveness of the various means and methods of vaccination against tularemia.

The research showed that aerosol immunization with tularemia dust vaccine provided a marked immunological reorganization of the organism of the innoculated persons. Thereby, the indices of the agglutination reaction were in a fixed dependence from the sizes of the inhaled doses of the preparation (See Table 2). Small doses (1 to 4.6 million) caused the least marked immunological improvements, the moderate doses (5.5 to 28 million) provided a distinct immunological effect and, finally, large doses resulted in the most intensive changes.

A study of the serums from people immunized cutaneously was carried out 30, 60 and 180 days after immunization. Thereby, it turned out that a positive agglutination reaction after 30 days was registered in 94 per cent of those innoculated with an average titer of 1 to 170. According to the titer of agglutinins for this period of time the results of cutaneous vaccination were 1.4 times lower than the results obtained by aerosol vaccination. After two months an agglutination reaction with an average titer of 1 to 197 was registered

for 94 per cent of the innoculated persons and, after six months, for 80 per cent of those innoculated with an average titer of 1 to 70.

Compared to the serum test, the skin-allergic test, in the opinion of the majority of the research specialists, is the more reliable test for determining the immunological reorganization of the organism of the persons innoculated against tularemia.

From the results of the study of the use of the skin-allergic test on the immunological improvements in people subjected to aerosol immunization (See Table 2), it is apparent that the indices for this reaction were relatively high. Thus, in individuals immunized with 1 to 4.6 million microbes, in 15 to 20 days after vaccination a positive skin-allergic test was observed in 57.8 per cent, and in 30 to 40 days in 86.4 per cent, and remained at a high level (75.2 per cent) up to half-a-year and even for a year's time (64 per cent) from the day of immunization. Among persons innoculated with 5.5 to 28 and 130 to 320 million microbes a positive skin-allergic reaction was observed after 15 to 20 and 30 to 41 days after vaccination in 82 to 100 per cent of those innoculated and after 90 to 110 days in 87 per cent. In 71 per cent of innoculated persons a positive skin-allergic reaction was found after 360 days.

Conclusions

1. The number of positive reactions in those innoculated by the aerosol method depended upon the size of the inhaled dose of vaccine.

2. Vaccine in doses of 5.5 to 28 million microbes, while causing an insignificant reaction, provided a sufficiently marked immunological reorganization of the organism of the innoculated persons. Therefore, at the present stage of study for aerosol immunization against tularemia, the given doses should, apparently, be taken as optimal.

3. The reactogenic nature of aerosol immunization with tularemia dust vaccine depends upon the initial immunological state of the organism of the persons innoculated and upon the dose of vaccine. During aerosol immunization of people with optimal doses of vaccine without preliminary immunological examination, the general reactogenic nature came to 2.82 per cent, and on a negative sero-allergic background to 1.19 per cent.

Table 1

Characteristics of the reactogenic nature of aerosol and cutaneous immunization with tularemia vaccine.

Группа иммунизированных	Доза вакцины (в млн. микробов)	Число иммунизированных	Число лиц с реакциями																	
			общие реакции								местные реакции				утрата трудоспособности					
			слабая		средней силы		сильная		всего		пневмония	фаринголаринготрахеобронхит	всего		абс.	%	продолжительность в сутках			
			абс.	%	абс.	%	абс.	%	абс.	%			абс.	%			1	2	3	4
1	2	3										13	14		15	16	17			
18 Иммунизированные аэрозольно на отрицательном фоне	1—4,6	223	1	0,42	1	0,42	1	0,42	3	1,27	—	2	2	0,9	2	0,9	1	1	—	—
	5,5—28	591	—	—	4	0,68	3	0,51	7	1,19	—	3	3	0,51	7	1,08	4	3	—	—
	130—320	119	18	15	6	5	5	4,2	29	24,2	—	10	10	8,3	8	6,7	2	2	2	—
19 Иммунизированные аэрозольно на положительном фоне	1—4,6	30	1	3,35	2	6,7	4	13,4	7	23,2	—	2	2	6,7	6	20	1	5	—	—
	5,5—28	12	3	25	1	8,4	1	8,4	5	41,5	—	1	1	8,4	2	16,8	1	—	1	—
20 Иммунизированные аэрозольно без снятия фона	1—4,6	497	2	0,4	8	1,6	5	1,01	15	3,01	—	7	7	1,4	12	2,42	4	5	1	—
	5,5—28	1 913	26	1,36	9	0,47	19	1,0	54	2,82	—	20	20	1,05	30	1,58	11	11	10	—
21 Всего . . .	1—28	3 266	33	1,01	25	0,76	33	1,01	91	2,78	—	35	35	1,07	59	1,81	22	25	12	—
22 Иммунизированные накожно на отрицательном фоне	130—320	119	18	15,13	6	5,04	5	4,2	29	24,2	—	10	10	8,3	8	6,72	2	4	2	—
		150	2	1,8	—	—	—	—	2	1,3	—	—	—	—	1	0,7	1	—	—	—
Иммунизированные накожно без снятия фона		110	2	1,95	2	1,95	—	—	4	3,9	—	—	—	—	3	2,7	1	2	—	—
21 Всего . . .		260	4	1,54	2	0,76	—	—	6	2,31	—	—	—	—	4	1,54	2	2	—	—

1. Immunized group; 2. Dose of vaccine (in millions of microbes); 3. Number immunized; 4. Number of individuals with reactions; 5. General reactions; 6. Weak; 7. Moderate; 8. Strong; 9. Total; 10. Local reactions; 11. Loss of capacity to work; 12. Pneumonia; 13. Pharyngolaryngotracheobronchitis; 14. Total; 15. Absolute; 16. Per cent; 17. Duration in days; 18. Immunized by the aerosol method on a negative background; 19. Immunized by the aerosol method on a positive background; 20. Immunized by the aerosol method without obtained background; 21. Immunized cutaneously on a negative background; 22. Immunized cutaneously without obtained background.

TABLE APPENDIX

Table 2

Immunological effectiveness of tularemia vaccine from the Number 15 (restored) strain during aerosol and cutaneous application.

Метод иммунизации 1	Доза вакцины (в млн. микробов) 2	Общее число исследований 3	Реакция агглютинации 4										Общее число исследований 16	Число положительных реакций аллергии в разные дни 17					Наличие иммунологической перестройки, регистрируемой хотя бы в одной реакции (через год после аэрозольной иммунизации) 18	
			15—20 дней 5		31—41 день		60—110 дней		180 дней		350 дней			15—20	30—41	90—110	180	350	число исследований 19	число лиц с наличием иммунологической перестройки 20
			число положительных реакций 6	средний титр 7	число положительных реакций 8	средний титр 9	число положительных реакций 10	средний титр 11	число положительных реакций 12	средний титр 13	число положительных реакций 14	средний титр 15								
21 Аэрозольно	1—4,6	63	10/28	1:6	6/9	1:11	—	—	—	—	16/28	1:9	411	71/128	70/81	—	76/101	64/101	28	23 (82%)
			35,7%		66,6%						57%			57,8%	86,4%		75,2%	64%		
	5,5—28	137	—	—	38/41	1:234	38/41	1:238	27/31	1:89	17/24	1:34	266	12/12	110/110	31/35	—	77/109	24	18 (85%)
					92,7%		92,7%		87,1%		71%			100%	100%	87%		71%		
	130—320	202	24/38	1:17	48/49	1:319	59/59	1:383	55/56	1:165	—	—	114	32/39	50/50	19/25	—	—	—	—
			79%		98%		100%		98,2%					82%	100%	76%				
22 Накожно		55	—	—	16/17	1:170	16/17	1:127	17/21	1:70	—	—	30	—	30/30	—	—	—	—	—
					94%		94%		80%						100%					

Note: Denominator -- number of individuals examined; numerator -- number of individuals with positive results.

1. Method of immunization; 2. Dose of vaccine (in millions of microbes); 3. Over-all number of tests; 4. Agglutination reaction; 5. 15 to 20 days; 6. Number of positive reactions; 7. Average titer; 8. Number of positive reactions; 9. Average titer; 10. Number of positive reactions; 11. Average titer; 12. Number of positive reactions; 13. Average titer; 14. Number of positive reactions; 15. Average titer; 16. Over-all number of tests; 17. Number of positive reactions of allergy at various days; 18. Presence of immunological reorganization registering even if in one reaction (in a year after aerosol immunization); 19. Number of tests; 20. Number of individuals with the presence of immunological reorganization; 21. By the aerosol method; 22. Cutaneously.